Agency for Healthcare Research and Quality
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NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline.

Bibliographic Source(s)

Dhesy-Thind S, Fletcher GG, Blanchette PS, Clemons MJ, Dillmon MS, Frank ES, Gandhi S, Gupta R, Mates M, Moy B, Vandenberg T, Van Poznak CH. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2017 Jun 20;35(18):2062-81. [125 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group

YES	Methodologist Involvement
▮▮▮▮▮	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▯	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▮	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▯▯▯	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▯▯	Rating the Strength of Recommendations
▮▮▮▮▮	**Specific and Unambiguous Articulation of Recommendations**
▮▮▮▯▯	**External Review**
▮▮▮▮▮	**Updating**

Recommendations

Major Recommendations

Preamble to Recommendations

The focus of this guideline is on the relapse and survival benefit of bone-modifying agents in nonmetastatic breast cancer. This guideline acknowledges that there is clear evidence for the use of bone-modifying agents such as bisphosphonates to reduce the risk of fragility fractures in at-risk populations (such as those with diagnosed low bone mass) and to treat metastatic cancer to the bone. None of the recommendations in this guideline are meant to restrict such use of bone-modifying agents in these situations, although they may influence the specific bisphosphonate selected when given for both bone health and adjuvant therapy. In addition, it is recognized that in many health care settings, bone-modifying agents such as bisphosphonates may currently be available, approved, and/or funded in specific doses and schedules only for the indications of improving bone mass and for treatment of bone metastases. As such, users of this guideline should consider available resources and access—as well as any other barriers within their local health care settings—to using the treatments recommended in this guideline for adjuvant breast cancer.

Qualifying statements are an integral part of the recommendations, and these should always be read and cited together.

Recommendation 1

It is recommended that administration of bisphosphonates as adjuvant therapy be considered for postmenopausal patients with breast cancer (including patients premenopausal before treatment who have menopause induced by ovarian suppression as detailed in Recommendation 5) deemed candidates for adjuvant systemic therapy.
The final decision of whether or not to administer bisphosphonates should be made during consultation between the patient and oncologist, taking into account patient and disease characteristics, including risk of recurrence, and weighing the potential benefits and risks (adverse effects).

Qualifying Statements for Recommendation 1

While the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis found benefit for bisphosphonates in all subgroups of postmenopausal patients, the absolute benefit was small. For patients with cancers assessed as having low risk of recurrence, the use of bisphosphonates may not result in clinically meaningful effect.
Considerations in deeming patients at high enough recurrence risk to receive adjuvant systemic therapy may also apply in deciding on bisphosphonate use. The majority of patients (83%) in the meta-analysis had also received adjuvant chemotherapy. Standard clinical and pathologic risk factors and recognized clinical tools may be used, where applicable, to estimate risk of recurrence and mortality.
Risk factors for osteonecrosis of the jaw (ONJ) and renal impairment should be assessed (Recommendation 6).
Patients should receive all other recommended breast cancer treatment, including surgery, radiation, and/or systemic therapy (see, for example, the National Guideline Clearinghouse [NGC] summary of the Cancer Care Ontario [CCO] guideline Optimal systemic therapy in early breast cancer).
There is no information to guide the use of bone-modifying agents for patients receiving systemic adjuvant therapy for completely resected local recurrence.

Recommendation 2

Zoledronic acid and clodronate are the recommended bisphosphonates for adjuvant therapy in breast cancer.
There is a need for more information comparing different agents and schedules, and it is recommended that such trials be conducted to establish the utility and optimal administration of other bisphosphonates for adjuvant therapy.

Qualifying Statements for Recommendation 2

Preliminary data from the SWOG S0307 trial suggest that clodronate, ibandronate, and zoledronic acid may provide similar disease-free survival (DFS) and overall survival (OS) benefit. However, as these data have, to date, only been published in abstract form, no definitive recommendations regarding ibandronate can yet be made. Full publication of the SWOG S0307 trial and results of the TEAM IIb (BOOG 2006-04) trial may support adjuvant ibandronate use. There is a large difference in ibandronate dosage between these trials (50 mg/day) and that used in treating osteoporosis (150 mg/month orally or 3 mg every 3 months intravenously). This dosage difference should be considered in future comparisons.
Clodronate has not been studied specifically in patients receiving aromatase inhibitors (AIs).
While the direct evidence from adjuvant trials is considered sufficient only for zoledronic acid and clodronate, others have hypothesized that any agent proven to reduce the risk of fragility fractures in at-risk populations (e.g., patients with postmenopausal or drug-induced osteoporosis) may be effective as adjuvant therapy for breast cancer. Given orally for osteoporosis treatment, alendronate has been used daily or weekly, while risedronate and ibandronate have been used daily, weekly, or monthly. Ibandronate has also been used intravenously. Less frequent administration, compared with clodronate, may make these preferable to patients if shown to be of adjuvant benefit. Further trials with adequate power and primary outcomes of DFS and OS are required to determine the optimal agent and dosing schedule.

Different adverse effect profiles, frequency and route of administration, cost, and regulatory approval may influence selection.

Recommendation 3

While results for adjuvant denosumab look promising, data are insufficient at this time to make any recommendation regarding its use in the adjuvant setting.
It is recommended that studies directly comparing denosumab with bisphosphonates and evaluating administration schedules be conducted.

Qualifying Statements for Recommendation 3

While the ABCSG-18 trial studied denosumab use in postmenopausal women with hormone receptor–positive breast cancer receiving AIs and found clear fracture reduction benefit, DFS results have only been reported as a conference presentation or abstract. As survival data have, to date, only been published in abstract form, no definitive recommendations can yet be made. Results are promising but limited compared with the body of evidence for bisphosphonates. Further results of the ABCSG-18 and D-CARE trials may provide stronger evidence for adjuvant denosumab use.

Recommendation 4

For patients who will receive adjuvant bisphosphonates (Recommendation 1), zoledronic acid at 4 mg intravenously over 15 minutes (or longer) every 6 months for 3 to 5 years or clodronate orally at 1,600 mg/day for 2 to 3 years are recommended. Different durations may be considered.
More research is recommended comparing different bone-modifying agents, doses, dosing intervals, and durations.

Qualifying Statements for Recommendation 4

In jurisdictions where the recommendation cannot be followed due to availability, similar doses and schedules of zoledronic acid or clodronate are considered reasonable.
The optimal dose and schedule of administration of zoledronic acid and clodronate have not been determined; however, the recommended doses and schedules have been found effective in many of the adjuvant breast cancer trials and result in fewer or less severe adverse effects than regimens used in patients with metastatic disease (i.e., 4 mg zoledronic acid every 3 to 4 weeks).
The optimal duration of adjuvant bone-targeted agents has not been determined; the recommendations reflect durations found effective in the EBCTCG meta-analysis and other trials included in the literature review. It is unclear whether there is benefit to longer-term administration, although studies indicate that the benefit of bisphosphonates continues after administration is stopped due to the persistence of the drug within the bone. There are concerns about adverse effects such as atypical bone fractures based on reports from the osteoporosis literature, and some osteoporosis recommendations allow a treatment holiday from bisphosphonates after 3 to 5 years for patients with a lower risk of fracture.
Administration of clodronate for >3 years or zoledronic acid for >5 years has not been evaluated in adjuvant trials, and, therefore, a recommendation of longer duration is not supported at this time. This limitation in the evidence may be especially relevant to patients receiving long-term endocrine therapy, as the NGC summary of the CCO guideline Optimal systemic therapy in early breast cancer includes recommendations for endocrine therapy for up to 10 years based primarily on results from the ATLAS, aTTom, and MA.17 trials.
The optimal timing to start bisphosphonates after diagnosis of breast cancer is unclear; however, most of the clinical trials started soon after surgery or chemotherapy.

Recommendation 5

For purposes of adjuvant bisphosphonate use, the definition of menopause should include both natural menopause (at least 12 months of amenorrhea prior to initiation of chemotherapy or endocrine therapy) and menopause induced by ovarian ablation or suppression (but not the cessation

of menses due to chemotherapy alone). In women age ≤60 years with a previous hysterectomy and ovaries left in place, luteinizing hormone, follicle-stimulating hormone, and serum estradiol should be in the postmenopausal range and measured prior to initiation of any systemic therapy to receive adjuvant bisphosphonates.

Qualifying Statements for Recommendation 5

As indicated in the NGC summary of the CCO guideline Optimal systemic therapy in early breast cancer, assessing menopausal status is difficult in patients age ≤60 years who experience amenorrhea secondary to chemotherapy or tamoxifen. Cessation of menses does not necessarily denote the absence of ovarian function, and premenopausal estradiol levels can be found in patients with transient chemotherapy-induced amenorrhea. In addition, hormone levels and the absence of menses are unreliable indicators of menopause during treatment with tamoxifen.
Some publications have suggested that patients experiencing chemotherapy-induced amenorrhea are at high risk for adverse bone effects and may be candidates for bone-modifying agents. Evidence is insufficient to address use of these agents as adjuvant treatment in this population.

Recommendation 6

A dental assessment is recommended, where feasible, prior to commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with prior to starting treatment, if possible. Patients should be informed of the risk of developing ONJ, especially with tooth extractions and other invasive dental procedures. Patients should inform their dental practitioner of their treatment. Patients with suspected ONJ should be referred to a dental practitioner with expertise in treating this condition. Recent guidelines or position papers by groups such as the International Task Force on Osteonecrosis of the Jaw, the American Association of Oral and Maxillofacial Surgeons, and the American Dental Association should be consulted.
Patients should have serum calcium measured prior to starting treatment. Patients receiving intravenous bisphosphonates (zoledronic acid) should be monitored for renal function prior to starting this treatment, and for serum calcium and increase in serum creatinine throughout the treatment period.
Calcium and vitamin D supplementation is recommended unless otherwise contraindicated. Oral bisphosphonates and calcium should not be taken concurrently; several monographs suggest an interval of at least 2 hours to allow for maximum absorption.
Symptoms such as ocular pain or loss of vision may be due to serious inflammatory conditions such as uveitis or scleritis and should be promptly evaluated by an ophthalmologist.

Qualifying Statements for Recommendation 6

The risk of ONJ increases with frequency, dose, and duration of bisphosphonate administration. Risk can be reduced with appropriate screening prior to treatment and modification of dental care. Risk of ONJ when bisphosphonates are administered, as suggested in Recommendation 4, is lower than for patients receiving higher doses or more frequent administration as is used for cancers with bone metastasis.
Some organizations advise dental assessment and care prior to any cancer treatment, preferably as soon as possible after diagnosis to allow time for dental procedures and adequate healing prior to treatment.
The CCO formulary monograph for zoledronic acid recommends "comprehensive dental evaluation of both hard and soft tissues before starting bisphosphonate treatment; undergo invasive dental procedures, if needed, before starting bisphosphonate treatment." U.S. Food and Drug Administration (FDA) prescribing information for zoledronic acid indicates that "cancer patients should maintain good oral hygiene and should have a dental examination with preventative dentistry prior to treatment with bisphosphonates."
It is unclear whether bone-modifying therapy should be withheld if invasive dental treatment is required. Some have hypothesized that withholding bone-modifying therapy may allow for better bone healing and suggested stopping treatment 2 months prior to oral surgery and delaying

restarting until osseous healing has occurred. The alternative view is that a short break in bisphosphonate administration will have no effect as bone effects of bisphosphonates are maintained for years after treatment stops.

Hypocalcemia is a known adverse effect of bisphosphonate treatment, especially with the higher doses and more frequent administration given to patients with metastatic cancer. It is relatively rare (<1%) at lower doses (Recommendation 4) in patients without pre-existing conditions such as renal insufficiency and who have adequate vitamin D status and calcium intake.

There is conflicting evidence as to whether inflammatory eye conditions are directly caused by bisphosphonates or in conjunction with some underlying inflammatory disease process; however, if not treated promptly, these conditions may lead to blindness. Discontinuation of bisphosphonates may be necessary.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Early or locally advanced (nonmetastatic) breast cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Evaluation

Risk Assessment

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Intended Users

Advanced Practice Nurses

Dentists

Physician Assistants

Physicians

Guideline Objective(s)

To make recommendations regarding the use of bisphosphonates and other bone-modifying agents as adjuvant therapy in patients with breast cancer

Target Population

Patients with early or locally advanced (nonmetastatic) breast cancer

Interventions and Practices Considered

1. Use of zoledronic acid and clodronate as adjuvant bone-targeted therapy
2. Use of other bone-modifying agents (denosumab) as adjuvant therapy (no recommendation made)
3. Doses, routes, and schedules for administration of bisphosphonates
4. Assessment of menopausal status (natural or induced by ovarian ablation or suppression) prior to commencement of bisphosphonate therapy
5. Dental assessment prior to commencement of bisphosphonate therapy
6. Informing patients of risk of osteonecrosis of the jaw (ONJ) prior to commencement of bisphosphonate therapy
7. Measurement of serum calcium and monitoring of renal function prior to commencement of bisphosphonate therapy
8. Calcium and vitamin D supplementation
9. Ophthalmological evaluation of ocular pain or loss of vision during bisphosphonate treatment

Major Outcomes Considered

- Breast cancer recurrence
- Distant recurrence
- Bone recurrence
- Distant recurrence outside bone
- Breast cancer mortality
- All-cause mortality
- Bone fractures
- Disease-free survival
- Overall survival

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Working Group of the Adjuvant Bisphosphonates in Breast Cancer Guideline Development Group (GDG) developed this evidentiary base to inform recommendations as part of a clinical practice guideline. The complete systematic review is included as Section 4 of the multipart Cancer Care Ontario (CCO) evidence-based series (see the "Availability of Companion Documents" field).

Research Questions

On the basis of the objectives of this guideline, the Working Group derived the following research questions:

Does administration of bisphosphonates or other bone-modifying agents as adjuvant treatment in

patients with breast cancer reduce metastasis and/or recurrence and improve survival?
Does effectiveness depend on patient or disease characteristics, especially age or menopausal status (either natural or induced menopause)?
Do effectiveness and adverse effects differ according to which bisphosphonate or bone-modifying agent is used?
What doses, duration of administration, and route (intravenous or oral) are optimal?

Search for Existing Guidelines

A search for existing guidelines was conducted using known guideline-developer Web sites and practice-guideline databases (refer to the Methodology Supplement [see the "Availability of Companion Documents" field]). No guidelines suitable for adaptation or endorsement were found. A search of the primary literature was required. A European consensus guideline was published subsequent to the literature search. It was evaluated as not meeting the criteria for endorsement; therefore, the guideline process was continued.

Literature Search Methods

During project planning, it was anticipated that the primary evidence base would be the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) individual patient data meta-analysis. Initial review of the EBCTCG publication revealed that meta-analysis included data from 26 trials. There were 24 additional trials that met their inclusion criteria but without data. Meta-analysis did not report data on adverse effects, nor did it provide references to publications for the included trials. It focused on bisphosphonates and, therefore, did not include other bone-modifying agents such as denosumab. EBCTCG only included trials that started before 2008. It was therefore considered necessary to conduct a full literature search to identify the included studies, determine the reason for missing data and whether they had been subsequently published, look for more recent data of included trials, identify ongoing or recently completed trials that started around 2008 or later—and were therefore excluded by EBCTCG—and to include trials of nonbisphosphonate bone-modifying agents.

Search for Systematic Reviews and Primary Literature

MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for the period 2005 to June 6, 2016. The search included terms for breast cancer, bisphosphonates or bone-modifying agents, and publication type. Abstracts from major conferences were searched separately for years that were not included in the above databases. Details about the literature review are provided in the Data Supplement (see the "Availability of Companion Documents" field).

Study Selection Criteria and Process

In the current literature review, studies included were randomized controlled trials (RCTs) that evaluated adjuvant or neoadjuvant use of bisphosphonates or other bone-modifying agents (primarily denosumab) compared with some control (none, placebo, other bisphosphonates, or different administration of the same bisphosphonate). Studies that were designed to measure cancer recurrence, survival, or distant metastasis (bone or visceral metastases) provided the strongest evidence. Studies that were primarily designed to evaluate bone-modifying effects such as bone mineral density (BMD) were excluded unless recurrence or survival outcomes were also part of the design (primary or secondary outcomes) and were reported in detail. To be included, studies had to evaluate at least 30 randomly assigned patients. RCTs were excluded that were designed to evaluate agents that primarily modify hormonal levels, such aromatase inhibitors (AIs), tamoxifen, or raloxifene, but which may have secondary bone effects. A review of the titles and abstracts that resulted from the search was conducted by one reviewer. The same reviewer looked at items that warranted full text review.

Inclusion criteria of the EBCTCG meta-analysis were broader and included any trial in which women were randomly assigned to bisphosphonate versus a control group without bisphosphonate. EBCTCG therefore included several additional trials that were designed primarily with BMD or similar outcomes and for which there was no published data on survival or recurrence outcomes. While some of these trials included large numbers of patients, there were few events of interest (recurrence or survival outcomes) and these

additional trials contributed little to the overall meta-analysis.

Literature Search Results

Of the systematic reviews and meta-analyses found, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) individual patient data meta-analysis was the most comprehensive and the main evidence source for the accompanying guideline, supplemented by additional RCTs and updated data that were found in the primary literature search. The EBCTCG meta-analysis included data from 26 trials, of which 14 met the inclusion criteria for this guideline on the basis of data in the corresponding publications and 12 did not, primarily because they were bone mineral density (BMD) studies that did not report recurrence or survival outcomes. The meta-analysis also listed an additional 24 trials for which data were not available.

The literature search combined with the EBCTCG meta-analysis found 27 trials (plus the 12 that did not meet the inclusion criteria for this guideline). In addition to trials with data included in the EBCTCG meta-analysis, the literature search also found results for the SWOG S0307 (abstract only) and ABCSG-18 trials, as well as a few small studies. While these publications mention at least some outcomes, complete publication or longer follow-up is still required for several of them. SWOG S0307 compared clodronate versus ibandronate versus zoledronic acid and, as such, gives data not in the EBCTCG meta-analysis. ABCSG-18 along with the ongoing D-CARE trial, provides data on denosumab, which is also not in the meta-analysis.

Refer to the Flow Diagram of Literature Search Results (Figure 4-1) in the Data Supplement (see the "Availability of Companion Documents" field) for an outline of the study selection process.

Number of Source Documents

A total of 39 studies (69 publications) were included.

Refer to the Flow Diagram of Literature Search Results (Figure 4-1) in the Data Supplement (see the "Availability of Companion Documents" field) for an outline of the study selection process.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

Data from the Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis and randomized controlled trials (RCTs) was extracted by one member of the Working Group. Ratios, including hazard ratios, were expressed with a ratio <1.0 indicating benefit of the experimental treatment (bisphosphonate). All extracted data and information were audited by an independent auditor.

Trial name(s) or location, trial identification/registration number, enrolment period, number of patients, patient characteristics, treatment arms or comparison, and outcomes stated in the trial design were summarized for all studies. As the EBCTCG meta-analysis results comprised the main evidence, detailed outcome data from most of the individual trials included in this meta-analysis were not extracted. Some exceptions were made when results in the meta-analysis appeared inconsistent or unclear, or an individual study appeared to contribute all the data for a subgroup analysis. During interpretation of the data, it became apparent that outcomes not included in the EBCTCG meta-analysis such as osteonecrosis of the jaw (ONJ) and other adverse effects were required, and these were added to the data extraction tables.

For studies not already included in the EBCTCG meta-analysis, recurrence, survival, and other outcome results were also extracted. Formal assessment of study quality was conducted only for trials that needed to be looked at in detail (i.e., in addition to the EBCTCG meta-analysis data). This also applied to major trials not included in the EBCTCG meta-analysis. To aid in assessing the quality of studies, the following details were looked for in the trial methods or publications: randomization method, allocation concealment and blinding, balanced baseline characteristics, industry funding, statistical power and target sample size, intention-to-treat analysis, description of patients who withdrew or were lost to follow-up, and whether the trial was terminated early (refer to Appendix 5 in the Data Supplement [see the "Availability of Companion Documents" field]).

Synthesizing the Evidence

Due to the existing EBCTCG meta-analysis on bisphosphonates, as well as ones on narrower topics of clodronate, zoledronic acid, and neoadjuvant zoledronic acid, no further meta-analysis was contemplated. However, a few of the subgroup results were recalculated after excluding one or more trials.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

To develop recommendations for the use of bisphosphonates and other bone-modifying agents as adjuvant therapy for patients with breast cancer, the Program in Evidence-Based Care (PEBC) of Cancer Care Ontario (CCO) and the American Society of Clinical Oncology's (ASCO's) Clinical Practice Guidelines Committee (CPGC) established a joint guideline panel.

Guideline Development Methods

The PEBC practice guidelines development cycle and the ASCO guideline development methods include a systematic review, interpretation of evidence, drafting of recommendations, internal review by content and methodology experts, and external review by clinicians and other stakeholders. Further details are provided below and in the Methodology Supplement (see the "Availability of Companion Documents" field).

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, addition of newer literature to the original evidence base—this is described in the PEBC Document Assessment and Review Protocol (see the "Availability of Companion Documents" field). PEBC guideline recommendations are based on clinical evidence and not on feasibility of implementation; however, a list of implementation considerations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook (see the "Availability of Companion Documents" field).

Guideline Developers

This guideline was developed by the Adjuvant Bisphosphonates in Breast Cancer Guideline Development Group (GDG), which was convened at the request of the CCO Breast Cancer Disease Site Group. The project was led by a smaller Working Group that was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology and health research methodology. Other members of the GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group.

Traditionally, guideline topics have been determined with CCO and then a search for existing guidelines is conducted to determine whether there are other guidelines that could be endorsed or adapted instead of creating a completely new guideline. The adaptation process can be quite long and costly. In discussion with ASCO, it was determined there would be benefit in codeveloping several guidelines, with either PEBC or ASCO taking the lead and the other organization being involved at various stages. In this manner, input of both groups would be given at an earlier stage in development such that later adaptation would not be required. For this codeveloped guideline, PEBC took the lead, including planning the project and its scope as well as constituting the Working Group. ASCO nominated four members to the Expert Panel and suggested some of the external reviewers. Per ASCO policy, a patient advocate and a representative from the ASCO Practice Guideline Implementation Network were included on the Expert Panel. Approval was sought from both the PEBC Report Approval Panel and the ASCO CPGC. Internal review consisted of review by the Expert Panel as well as these two approval groups. Additional details regarding the review process, including concerns or comments of the reviewers and how they were addressed, are given in the Methodology Supplement (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Guideline Review and Approval

Internal Review - Program in Evidence-Based Care (PEBC)

All guidelines are evaluated by the Guideline Development Group (GDG) Expert Panel and the PEBC Report Approval Panel (RAP), which together are considered the internal review bodies for PEBC documents. For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must have cast a vote indicating they approved the document, or abstained from voting for a specified reason; of those that voted, 75% must have approved the document. In addition, the RAP, a three-person panel with methodology expertise, was required to unanimously approve the document. The Expert Panel and RAP members could specify that approval was conditional, and that changes to the document were required. If substantial changes were subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

Review – American Society of Clinical Oncology (ASCO)

As part of the collaboration with ASCO, the ASCO Clinical Practice Guidelines Committee (CPGC) was also required to approve the document before it could be released as a joint PEBC-ASCO guideline. Due to differences in structure of PEBC/Cancer Care Ontario (CCO) and ASCO guidelines, the ASCO CPGC approved a document with the same content and recommendations as other reviewers but rearranged according to usual ASCO and *Journal of Clinical Oncology* requirements.

Refer to the Methodology Supplement (see the "Availability of Companion Documents" field) for further discussion of the internal guideline review process and voting results.

External Review

Feedback on the approved draft guideline was obtained from content experts and the target users through two processes. Through the targeted peer review, several individuals with content expertise were identified by the GDG and ASCO and asked to review and provide feedback on the guideline document. Through professional consultation, relevant care providers and other potential users of the guideline were contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation was intended both to gather feedback and to facilitate the dissemination of the final guidance report to Ontario practitioners.

The ASCO Clinical Practice Guideline Committee approved this guideline on September 15, 2016. The CCO RAP approved the update on June 15, 2016.

Refer to the Methodology Supplement for further discussion of the external guideline review process and results.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized controlled trials (RCTs), meta-analyses, and systematic reviews.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Adjuvant bisphosphonates were found to reduce bone recurrence and improve survival in postmenopausal patients with nonmetastatic breast cancer. In this guideline, postmenopausal includes patients with natural menopause or that induced by ovarian suppression or ablation. Absolute benefit is greater in patients who are at higher risk of recurrence, and almost all trials were conducted in patients who also received systemic therapy. Refer to the "Qualifying Statements" in the "Major Recommendations" field for further details on benefits of specific recommendations.

Potential Harms

- One of the more serious adverse effects of bisphosphonate treatment is osteonecrosis of the jaw (ONJ). To lower the risk, many of the more recent trials excluded patients with recent or planned dental or jaw surgery (extraction or implants).
- Postmarketing surveillance has reported rare adverse effects of bisphosphonates, such as

inflammatory eye reactions, renal toxicity, and atypical femoral fractures. The risk of renal toxicity and atypical femoral fractures may be increased at higher dosing and prolonged use. Acute inflammatory eye reactions, including conjunctivitis, uveitis, scleritis, episcleritis, and keratitis, are rare but warrant prompt evaluation by an ophthalmologist. Treatment is commonly with ophthalmic corticosteroids.

- Other transient acute-phase reactions for intravenous administration occur in approximately one third of patients and include low-grade fever, fatigue, arthralgia or myalgia, nausea, and increased bone pain. One trial also reported mild transient adverse events with zoledronic acid, including bone pain, pyrexia, and acute-phase reaction.
- Oral administration has low absorption (<5%), and, therefore, high doses are required; these can cause esophagitis and other gastrointestinal events (mucositis, nausea, vomiting, and diarrhea). Clodronate is administered in large capsules taken daily, which may be difficult to swallow. Clodronate and ibandronate are to be taken on an empty stomach and require the patient to remain upright for at least 30 minutes.
- Hypocalcemia is a known adverse effect of bisphosphonate treatment, especially with the higher doses and more frequent administration given to patients with metastatic cancer. It is relatively rare (<1%) at lower doses in patients without pre-existing conditions such as renal insufficiency and who have adequate vitamin D status and calcium intake.

Contraindications

Contraindications

- Oral bisphosphonates and calcium should not be taken concurrently; several monographs suggest an interval of at least 2 hours to allow for maximum absorption.
- The guideline developers note that no attempt has been made to list all the potential adverse effects of drugs that are mentioned in the guideline, nor contraindications to their use. Drug monograms, formulary, or other prescribing information should be consulted.

Qualifying Statements

Qualifying Statements

Guideline Disclaimers

Care has been taken in the preparation of the information contained herein. Nevertheless, any person seeking to consult the report or apply its recommendations is expected to use independent medical judgment in the context of individual clinical circumstances or to seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.

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This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki/ to submit new evidence.
Refer to the "Limitations of the Research and Future Research" section of the original guideline document for additional qualifying information.

See the original guideline document for qualifying statements related to each recommendation.

Implementation of the Guideline

Description of Implementation Strategy

- It is desirable to have multiple agents with different modes of administration (Recommendation 2).
- As with any novel therapy or new indication for existing medications, cost, access, funding, and drug approval need to be considered in the implementation of treatment recommendations. As mentioned in the preamble of the original guideline document, several health care settings currently may only have access to bone-modifying agents to improve bone density or for treatment of metastatic cancer. As such, drug formularies and governing bodies may need to revise approved dose and scheduling parameters for these relevant medications before clinicians may be able to use them. As examples in North America:
    - Zoledronic acid has recently been added to the Cancer Care Ontario (CCO) Drug Formulary (April 2016) for adjuvant treatment of breast cancer in postmenopausal women. Clodronate thus far only has Health Canada Approval for the management of hypercalcemia of malignancy and for treatment of bone metastases, and is included in the CCO Formulary and British Columbia Cancer Agency Cancer Drug Manual for these purposes.
    - Zoledronic acid is approved in the United States for treatment of low bone mass and metastatic disease, and clodronate is not available.
    - Ibandronate is not currently approved for use in Canada. It is approved by the U.S. Food and Drug Administration for the prevention or treatment of postmenopausal osteoporosis.
    - Direct patient cost and health system resource impact should be considered in implementing such recommendations.

American Society of Clinical Oncology (ASCO) guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers as well as to provide adequate services in the face of limited resources. The Bottom Line Box in the original guideline document was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

Also refer to the "Preamble to Recommendations" in the "Major Recommendations" field and the "Preamble and Implementation Considerations" in the original guideline document for additional discussion of implementation.

For additional information on the ASCO implementation strategy, please see the ASCO Web site .

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Dhesy-Thind S, Fletcher GG, Blanchette PS, Clemons MJ, Dillmon MS, Frank ES, Gandhi S, Gupta R, Mates M, Moy B, Vandenberg T, Van Poznak CH. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2017 Jun 20;35(18):2062-81. [125 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

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Financial Disclosures/Conflicts of Interest

Conflicts of Interest

The Working Group and Expert Panel were assembled and managed in accordance with the conflict of interest (COI) policies of the Program in Evidence-Based Care (PEBC) and the American Society of Clinical Oncology (ASCO). All members of the Expert Panel completed the PEBC COI disclosure form. Declared conflicts were evaluated against both PEBC and ASCO COI policies, and the authors met the requirements for both. Potential Report Approval Panel and ASCO Clinical Practice Guidelines Committee (CPGC) members with any COIs (on the basis of the Cancer Care Ontario [CCO] and ASCO COI policies, respectively) were not eligible to review or approve the guideline; those involved in the process had no conflicts. Targeted external reviewers were required to complete a COI form; conflicts were not a barrier to participation. Potential conflicts for all participants are given in the full document on the CCO Web

site. For purposes of publication, authors completed an additional *Journal of Clinical Oncology*/ASCO COI form, and declarations are available at ascopubs.org/journal/jco .

Authors' Disclosures of Potential Conflicts of Interest

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc .

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Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Clinical Oncology Web site .

Availability of Companion Documents

The following are available:

- Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: systematic review. Data supplement. Alexandria (VA): American Society of Clinical Oncology; 2017. 62 p. Available from the Journal of Clinical Oncology Web site .
- Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. Methodology supplement. 2017. 6 p. Available from the Journal of Clinical Oncology Web site .
- Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2017. 21 p. Available in PowerPoint and PDF from the ASCO Web site.
- Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. Summary of recommendations. Alexandria (VA): American Society of Clinical Oncology; 2017. 7 p. Available from the ASCO Web site .
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available from the Cancer Care Ontario (CCO) Web site .
- Program in Evidence-based Care methods handbook. Toronto (ON): Cancer Care Ontario (CCO); 2017 Mar 3. Available from the Program in Evidence-based Care (PEBC) Toolkit Web site .
- Program in Evidence-based Care document assessment and review protocol. Toronto (ON): Cancer Care Ontario (CCO); 2015 Apr 16. 15 p. Available from the CCO Web site .

Patient Resources

The following is available:

- Breast cancer. Patient information. 2017. Available from the Cancer.Net Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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